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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,295	BARBOSA ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 and 15-21 are pending in the application.

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on January 17, 2006 is acknowledged. The traversal is on the ground(s) that it would not be a serious burden if the definition of J^1 is extended to cover both O or S. Upon further consideration Groups I and II have been combined to include 6,7-dihydro-pyrimido[5,4-b][1,4]oxazines and 7,8-dihydro-6H-pyrimido[5,4-b][1,4]thiazines.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-10 and 15-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is the Wands factors, which are used to evaluate the enablement question. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace pyrimido[5,4-b][1,4]oxazine and pyrimido[5,4-b][1,4]thiazine compounds. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active in vivo. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention.

The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claims 1-10 and 15-21. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

3. Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5)

the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

HOW TO USE: Claim 19 is to a method of treating a disease, which is associated with leukocyte activation. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of the method claims are not adequately enabled solely based on inhibition of leukocyte activation provided in the specification. Diseases and/or disorder(s) known to be associated with leukocyte activation inhibitory activity include transplant rejection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed 6,7-dihydro-pyrimido[5,4-b][1,4]oxazines and 7,8-dihydro-6H-pyrimido[5,4-b][1,4]thiazines compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification has no working examples on the use of the substituted 6,7-dihydro-pyrimido[5,4-b][1,4]oxazines and 7,8-dihydro-6H-pyrimido[5,4-b][1,4]thiazines,

etc. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of transplant rejection, graph verses host disease, rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease, ischemic or reperfusion injury, cell proliferation, psoriasis, etc.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 1-10 and 15-21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $T^{17}C(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (i).

b) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $T^{17}C(O)_tN(T^{11})T^{10}$-$SO_3H$. See the definition of T^1-T^9 labeled paragraph (i).

c) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $S(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (i).

d) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $-T^{12}-N(T^{16})-T^{15}-T^{10}$ where T^{15} is a divalent moiety. See the definition of T^1-T^9 labeled paragraph (i).

e) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $T^{17}C(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (ii).

f) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $S(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (ii).

g) Claims 1-5, 9, 10 and 15-20 are vague and indefinite in that it is not known what is meant by the moiety $-T^{12}-N(T^{16})-T^{15}-T^{10}$ where T^{15} is a divalent moiety. See the definition of T^1-T^9 labeled paragraph (ii).

h) Claim 3 recites the limitation "0-4" in the third moiety in line 3. There is insufficient antecedent basis for this limitation in the claim.

i) Claim 3 recites the limitation "haloalkyl" in the definition of Y^5. There is insufficient antecedent basis for this limitation in the claim.

j) Claim 5 recites the limitation "$-NHC(O)T^{10}$" in the definition or R^4. There is insufficient antecedent basis for this limitation in the claim.

k) Claim 5 is vague and indefinite in that it is not known what is meant by the moiety $T^{12}N(T^{16})-T^{15}-T^{10}$ where T^{15} is a divalent moiety. See the definition of R^4.

l) Claim 5 recites the limitation "$-NHC(O)T^{10}$" in the definition of the substituents on the ring formed by R^3 and R^4 together. There is insufficient antecedent basis for this limitation in the claim.

m) Claim 5 is vague and indefinite in that it is not known what is meant by the moiety $T^{12}N(T^{16})-T^{15}-T^{10}$ where T^{15} is a divalent moiety. See the definition of the substituents on the ring formed by R^3 and R^4 together.

n) Claim 5 recites the limitation "wherein each heterocyclo or heteroaryl is further optionally substituted by one to three groups independently selected from cyano, oxo, hydroxyl, alkyl, halo, haloalkyl and -OT^{10m}" in the definition of the substituents on the ring formed by R^3 and R^4 together. There is insufficient antecedent basis for this limitation in the claim.

o) Claim 5 recites the limitation "-$C(O)_tNHS(O)_t(T^{11})$" in the definition of the substituents of R^5. There is insufficient antecedent basis for this limitation in the claim.

p) Claim 5 recites the limitation "-$C(O)_tT^{11m}$" in the definition of the substituents of R^5. There is insufficient antecedent basis for this limitation in the claim.

q) Claim 5 recites the limitation "wherein each heterocyclo or heteroaryl is further optionally substituted by one to three groups selected from cyano, oxo, hydroxyl, alkyl, halo, haloalkyl and -OT^{10m}" in the definition of the substituents on R^5. There is insufficient antecedent basis for this limitation in the claim.

r) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety $T^{17}C(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (i).

s) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety $S(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (i).

t) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety -T^{12}-$N(T^{16})$-T^{15}-T^{10} where T^{15} is a divalent moiety. See the definition of T^1-T^9 labeled paragraph (i).

u) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety $T^{17}C(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (ii).

v) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety $S(O)_tN(T^{11})T^{10}$ which fails to indicate the point of attachment. See the definition of T^1-T^9 labeled paragraph (ii).

w) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety $-T^{12}-N(T^{16})-T^{15}-T^{10}$ where T^{15} is a divalent moiety. See the definition of T^1-T^9 labeled paragraph (ii).

x) Claims 6-8 are vague and indefinite in that it is not known what is meant by the moiety $S(O)_tN(T^{11})T^{22}$ which fails to indicate the point of attachment. See the definition of T^{11}, T^{14}, T^{15}, T^{16} and T^{19} labeled paragraph (ii).

y) Claim 7 recites the limitation "-NH-$CH_2CH_2NHC(=O)CH_3$" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 4th moiety in line 3 on page 12.

z) Claim 7 recites the limitation "3-$CH_3C(=O)$NHpyrrolidin-1-yl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 7th moiety in line 5 on page 12.

aa) Claim 8 recites the limitation "4-$CH_3CH_2SO_2$NHbenzyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 2nd moiety in line 2 on page 14.

ab) Claim 8 recites the limitation "4-$CH_3SO_2NHC(=O)$benzyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 3rd moiety in line 2 on page 14.

ac) Claim 8 recites the limitation "4-$CH_3CH_2CH_2SO_2NH$benzyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 4th moiety in line 2 on page 14.

ad) Claim 8 recites the limitation "4-$(CH_3)_2CHSO_2NH$benzyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 1st moiety in line 3 on page 14.

ae) Claim 8 recites the limitation "4-$CH_3CH_2SO_2NH$benzyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim. See the 3rd moiety in line 3 on page 14.

af) Claim 16 is vague and indefinite in that claim 21 is not a composition claim.

ag) Claim 16 is vague and indefinite in that it is dependent upon a canceled claim.

ah) Therapeutic agent in claims 17 and 18 is a relative terms, which renders the claim indefinite. The various specific terms of claim 18 "PDE4 inhibitors, consisting of NSAIDs", "COX-2 inhibitors", "TNF-α inhibitors", "beta-2 agonists", "anti-cholinergic agents", "steroids", etc. are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope

of the invention. The nature of the composition consisting of the compounds of formula I and an additional active ingredient, which is as a therapeutic agent.

ai) Claims 17 and 18 are substantial duplicates of claim 15. A statement of intended use is not given material weight. Note In re Tuominen 213 USPQ 89

aj) Claims 17 and 19 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by the inhibition of leukocyte activation. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in a 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to

work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital - should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of who are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in schizophrenia, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a

specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

ak) Claim 19 is vague and indefinite in that it is not known what is meant by "at least one composition of claim 1" where claim 1 is not a composition claim.

Claim Objections

5. Claim 16 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be stated in the alternative. See MPEP § 608.01(n).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
March 13, 2006